

Visible-Light-Promoted Radical Cascade Cyclization of Indole Derivatives: A Convergent Approach toward Functionalized Polycyclic Heterocycles

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Abstract

Indole and fused indole frameworks are prominent structural motifs in natural goods, pharmaceuticals and physiologically active heterocycles. The synthesis of complex indole alkaloids via classical routes generally involves many functional-group modifications and consecutive bond-forming reactions. Radical cascade reactions present a promising alternative, as numerous C–C and C–heteroatom bonds can be potentially generated in a single operation. Recent progress in visible-light photoredox catalysis has shown efficient generation of radicals under mild conditions, intramolecular radical addition to indoles, radical cascade synthesis of indolo[2,1-a]isoquinolines, photocatalytic alkoxyacylation/cyclization, and sulfonyl radical-triggered relay cyclization. We describe herein a convergent visible-light-promoted radical cascade approach for the construction of functionalized polycyclic indole derivatives. The approach is meant to couple radical production with intramolecular cyclization and to install synthetically beneficial ester or sulfonyl functionalities. A systematic study involving photocatalyst screening, solvent optimization, irradiation conditions, substrate variation, radical trapping, and spectroscopic characterization is proposed. The strategy is inspired by established radical approaches toward mersicarpine and goniomitine as well as modern photoredox methods for indole functionalization. The proposed methodology may provide a concise and modular route toward structurally diverse polycyclic indoles and related heterocyclic scaffolds.

Keywords: Indole; photoredox catalysis; radical cascade; visible light; cyclization; alkoxyacylation; sulfonylation; indolo[2,1-a]isoquinoline; heterocycles.

Introduction

Indole is one of the most versatile nitrogen-containing heterocyclic scaffolds in organic chemistry. Its electronic structure allows it to participate in a wide variety of electrophilic, nucleophilic, radical, and transition-metal-mediated reactions. Consequently, indole derivatives are widely found in natural products and medicinally important compounds.

The discovery of efficient methodologies for the synthesis of polycyclic indole frameworks remains an important goal in synthetic organic chemistry. A particularly attractive strategy is cascade radical cyclization, in which radical addition to an unsaturated bond is followed by intramolecular cyclization. Such transformations can rapidly increase molecular complexity while reducing the number of individual synthetic steps. The relevance of radical cascade chemistry to complex indole synthesis was demonstrated in the formal synthesis of (±)-mersicarpine by Biechy and Zard (2009), who employed a flexible radical addition–cyclization strategy to construct a polycyclic indole framework.

A major development in radical chemistry has been the application of photoredox catalysis. Tucker et al. (2010) demonstrated that tris(2,2'-bipyridyl)ruthenium dichloride could promote radical cyclizations onto indoles and pyrroles under visible-light irradiation at room temperature. More broadly, cascade radical cyclization has emerged as an effective strategy for the synthesis of carbo- and heterocyclic frameworks (Liao et al., 2021).

Wei et al. (2019) reported a photocatalyzed synthesis of indolo[2,1-a]isoquinoline derivatives through visible-light-induced radical cascade cyclization. Subsequently, Chen et al. (2022) developed a photocatalytic alkoxyacylation/cyclization approach for the synthesis of ester-substituted indolo[2,1-a]isoquinolines.

Yang et al. (2022) reported a visible-light-induced sulfonyl radical-triggered relay cyclization of indole and pyrrole derivatives, providing sulfonylated heterocyclic products. These studies demonstrate the potential of photoredox catalysis for generating and manipulating radical intermediates in the construction of structurally complex indole-based heterocycles.

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The chemistry of complex indole alkaloids also provides inspiration for the proposed research. Fischer indolization has been explored as a strategic approach toward the total synthesis of (–)-goniomitine (Pritchett et al., 2017), while bio-inspired fragmentation strategies have provided alternative routes to indolones, 2-quinolinones, and (–)-goniomitine (Li et al., 2017).

A thorough investigation of photocatalyst screening, solvent optimization, irradiation conditions, substrate scope, radical trapping, and spectroscopic characterization is proposed. The methodology is based on documented radical approaches to mersicarpine and goniomitine, together with contemporary photoredox techniques for the functionalization of indoles. The proposed methodology may provide a concise and modular approach to structurally diverse polycyclic indoles and related heterocyclic scaffolds. Taken together, these studies suggest that visible-light-mediated radical generation and cascade cyclization can serve as a powerful platform for constructing complex indole architectures.

Research Problem

Although radical chemistry of indoles has advanced greatly, the majority of synthetic methods are based on a certain radical precursor or a type of product. In this study, we address the research potential of developing a common indole-based radical cascade platform, where the radical precursor can be modified to incorporate diverse functional groups into the polycyclic result.

Materials and Methods

Commercially available indoles, radical precursors, solvents, bases and photocatalysts should be used where possible. Solvents should be dried or purified according to the requirements of the reaction.

Photochemical reaction setup: The reaction should be performed in a sealed glass vial equipped with a magnetic stir bar. A blue LED source in the visible region should be used as the initial irradiation source. The reaction vessel should be positioned at a reproducible distance from the LED and temperature should be monitored.

General proposed procedure: The indole-derived substrate, radical precursor and photocatalyst are combined in a suitable solvent under an inert atmosphere where required. The reaction mixture is irradiated with visible light while stirring. Reaction progress is monitored using TLC, LC-MS or GC-MS where appropriate. After completion, the mixture is concentrated and purified using column chromatography or another suitable purification method.

Exact quantities, catalyst loading, irradiation time, wavelength, distance and purification conditions must be determined experimentally and reported from the actual laboratory experiment.

Reaction Optimization

A systematic optimization study should examine photocatalyst identity, light wavelength, solvent, atmosphere, additive/base, reaction time and catalyst loading. Suggested control experiments include reactions without photocatalyst, without light, and under air versus inert atmosphere.

Important: Numerical conversion and yield values must be obtained experimentally and should not be fabricated.

Substrate Scope

After identifying suitable conditions, the reaction should be evaluated with electron-rich, electron-deficient, sterically modified and N-substituted indoles. Representative radical partners should include sulfonyl, alkoxycarbonyl and selected carbon-centered radical precursors.

A final substrate-scope table should report substrate, substituent, radical precursor, isolated product, isolated yield, diastereomeric ratio where applicable, and HRMS data.

Alkoxycarbonylation/Cyclization

Chen et al. demonstrated that visible-light photoredox catalysis can accomplish direct alkoxycarbonylation/cyclization to provide ester-substituted indolo[2,1-a] isoquinolines [5]. The

present work proposes to investigate whether analogous radical carbonylation chemistry can be incorporated into a broader cascade platform. The ester group provides a synthetic handle for hydrolysis, amidation, reduction, transesterification and further carbon–carbon bond formation.

Sulfonyl Radical Cyclization

Yang et al. demonstrated visible-light-induced sulfonyl radical-triggered relay cyclization of indole and pyrrole derivatives [6]. The proposed research will investigate whether sulfonyl radicals can similarly be incorporated into the selected polycyclic indole framework. Potential sulfonyl groups include arylsulfonyl, alkylsulfonyl and substituted arylsulfonyl groups.

Mechanistic Studies

Mechanistic experiments should include dark controls, photocatalyst controls, radical-trapping experiments using TEMPO or another suitable reagent, oxygen controls, and, where feasible, radical-clock experiments. Suppression of the reaction in the dark or without the photocatalyst, and/or observation of radical-trapping products, would provide evidence relevant to a radical pathway.

Analytical Characterization

All isolated compounds should be fully characterized using ¹H NMR, ¹³C NMR, HRMS and FT-IR where appropriate. Melting points should be reported for crystalline products. If asymmetric products are obtained, optical rotation and chiral HPLC should be considered. Single-crystal X-ray diffraction may be used when suitable crystals are obtained.

NMR reporting format: δ (ppm), multiplicity, integration and J values (Hz). HRMS should report calculated and found m/z values. Numerical spectral data must be obtained experimentally.

Proposed Mechanism

The proposed catalytic cycle is: visible light $\rightarrow$ excited photocatalyst $\rightarrow$ single-electron transfer $\rightarrow$ radical generation $\rightarrow$ addition to alkene $\rightarrow$ carbon-centered radical $\rightarrow$ intramolecular addition to indole $\rightarrow$ cyclized radical intermediate $\rightarrow$ electron/proton transfer $\rightarrow$ polycyclic indole product.

The photoredox generation of radicals and their subsequent cyclization onto indoles is consistent with the precedent established by Tucker et al. [2]. The exact redox steps and identity of the radical intermediate must be established experimentally.

Expected Results and Discussion Framework

The proposed research is expected to provide information regarding photocatalytic efficiency, substrate tolerance, radical-source diversity and functional-group compatibility. Electron-rich and electron-deficient indoles will help define electronic requirements, while variation of radical precursors will establish the modularity of the methodology.

Significance of the Proposed Work

The proposed methodology combines radical cascade chemistry, visible-light photoredox catalysis, fused indole construction and functional-group installation. It is intended to provide a modular approach to structurally diverse polycyclic indoles. The strategy is supported by established literature precedent in photoredox radical cyclization, indolo[2,1-a]isoquinoline synthesis, alkoxycarbonylation/cyclization and sulfonyl radical relay chemistry [2,4–6].

Advantages of the Proposed Method

1. Convergent synthesis.
2. Mild visible-light activation.
3. Rapid molecular-complexity generation.
4. Ester or sulfonyl functional-group installation.
5. Modularity through variation of radical precursors.
6. Mechanistic accessibility through photochemical controls and radical-trapping studies.

Potential Applications

Functionalized polycyclic indoles generated through this methodology could potentially serve as intermediates for natural-product synthesis, medicinal chemistry, heterocyclic library development, synthesis of indole alkaloid analogues, structure–activity relationship studies, ester transformations and sulfone functional-group manipulation.

Limitations and Future Work

Highly electron-deficient indoles may exhibit reduced reactivity, while steric congestion around the radical acceptor may interfere with cyclization. Competing radical pathways may also reduce selectivity.

Future research should investigate asymmetric versions of the cascade, enantioselective photocatalysis, additional radical precursors, late-stage functionalization of complex indoles, photochemical scale-up, continuous-flow photochemistry and biological evaluation of selected products.

Conclusion

A convergent visible-light-promoted radical cascade strategy has been proposed for the synthesis of functionalized polycyclic indoles. The research concept integrates established advances in radical indole chemistry, photoredox catalysis, visible-light radical cascade cyclization, alkoxycarbonylation/cyclization and sulfonyl radical relay chemistry.

The central objective is to establish a modular reaction platform in which radical generation, addition to an unsaturated acceptor and intramolecular indole cyclization occur in a controlled sequence. Ester and sulfonyl groups are proposed as representative functionalities because they provide valuable synthetic handles for subsequent molecular diversification.

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